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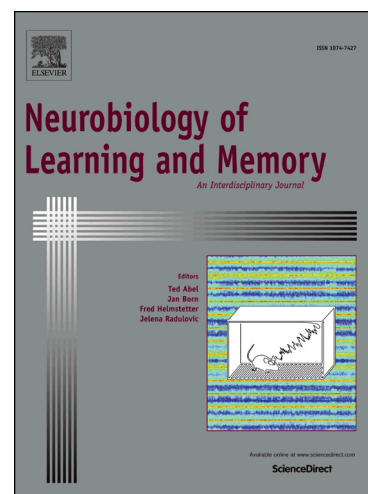
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## **The ‘Affect Tagging and Consolidation’ (ATaC) Model of Depression Vulnerability**

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## Abstract

Since the 1960's polysomnographic sleep research has demonstrated that depressive episodes are associated with REM sleep alterations. Some of these alterations, such as increased REM sleep density, have also been observed in first-degree relatives of patients and remitted patients, suggesting that they may be vulnerability markers of major depressive disorder (MDD), rather than mere epiphenomena of the disorder. Neuroimaging studies have revealed that depression is also associated with heightened amygdala reactivity to negative emotional stimuli, which may also be a vulnerability marker for MDD. Several models have been developed to explain the respective roles of REM sleep alterations and negatively-biased amygdala activity in the pathology of MDD, however the possible interaction between these two potential risk-factors remains uncharted. This paper reviews the roles of the amygdala and REM sleep in the encoding and consolidation of negative emotional memories, respectively. We present our 'affect tagging and consolidation' (ATaC) model, which argues that increased REM sleep density and negatively-biased amygdala activity are two separate, genetically influenced risk-factors for depression which interact to promote the development of negative memory bias – a well-known cognitive vulnerability marker for depression. Predictions of the ATaC model may motivate research aimed at improving our understanding of sleep dependent memory consolidation in depression aetiology.

*Keywords:* rapid eye movement (REM) sleep; amygdala; emotional memory bias; emotional memory consolidation; depression

## 1. Introduction

Depression is a complex affective disorder associated with symptoms such as sad mood, fatigue, anhedonia and suicidal ideation (American Psychiatric Association, 2013). Major depressive disorder (MDD) is the leading cause of disability in developed countries, and is experienced by around 20% of individuals at some point in their life (Kessler et al., 2003). It is recognised that MDD is a multifactorial disease, meaning that it may be caused by a wide range of hereditary and environmental factors (Bembnowska & Joško-Ochojska, 2015).

Since the publication of Beck's cognitive model of depression (Beck, 1967), a large body of empirical evidence has emerged demonstrating a relationship between negative biases in cognition and depression (Bourke, Douglas, & Porter, 2010; Everaert, Duyck, & Koster, 2014; Gaddy & Ingram, 2014; Naudin et al., 2014). For example, relative to healthy controls, individuals with depression tend to exhibit superior recall performance for negative emotional information (Everaert et al., 2014; Gaddy & Ingram, 2014). In accordance with Beck's model, findings from longitudinal cohort studies and cognitive bias modification (CBM) studies have demonstrated that this 'negative memory bias' can play a causal role in the onset and maintenance of depressive symptoms (Newby, Lang, Werner-Seidler, Holmes, & Moulds, 2014; Sumner, Griffith, & Mineka, 2010). Memory bias in MDD is thought to be related to altered patterns of functional activity in the amygdala, a limbic structure implicated in the encoding of emotional material (Elliott, Zahn, Deakin, & Anderson, 2011).

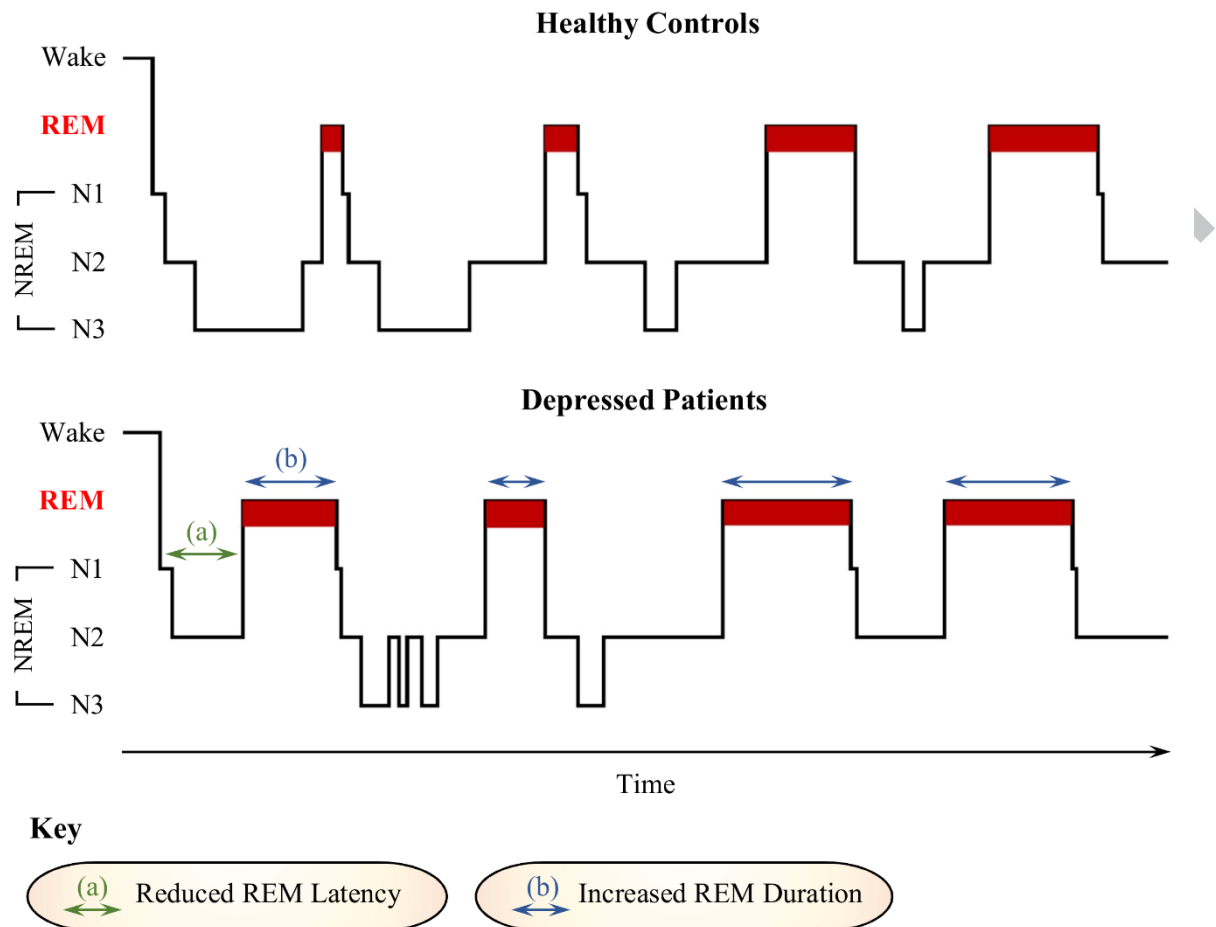
A separate line of research reveals that MDD vulnerability and depressive episodes are reliably associated with increased REM sleep density and increased REM sleep duration, respectively (Luik, Zuurbier, Whitmore, Hofman, & Tiemeier, 2015; Palagini, Baglioni,

Ciapparelli, Gemignani, & Riemann, 2013; Pillai, Kalmbach, & Ciesla, 2011). Studies in healthy participants demonstrate that both REM sleep density and REM sleep duration during the consolidation interval following encoding of emotional and neutral stimuli correlates positively with memory performance for negative but not neutral stimuli (Gilson et al., 2015; Nishida, Pearsall, Buckner, & Walker, 2009; Payne, Chambers, & Kensinger, 2012). These findings support the notion that REM sleep plays a selective role in the consolidation of negative emotional memories (Goldstein & Walker, 2014; Walker & van der Helm, 2009). Considered alongside evidence for REM sleep alterations in MDD vulnerability and depressive episodes, this may imply a relationship between REM sleep alterations and the emotional memory biases central to the onset and maintenance of depression.

The aim of this paper is to evaluate evidence supporting the hypothesis that the REM sleep alterations associated with MDD vulnerability and depressive episodes may promote the onset and maintenance of MDD through the development of negative memory bias. We provide an overview of the existing evidence for increased REM sleep density and duration, and altered patterns of functional amygdala activity, in the pathology of depression; before reviewing their roles in emotional memory formation. We then integrate these two lines of research by introducing our ‘affect tagging and consolidation’ (ATaC) model, which proposes that interactive effects between altered patterns of functional amygdala activity in response to emotionally salient stimuli and REM sleep alterations could result in the development of emotional memory bias, potentially causing or maintaining depression. We discuss the possible genetic basis of these two mechanisms and suggest future research which should be conducted in order to validate the ATaC model.

## **2. The Role of REM Sleep in Depression**

Disturbances in sleep consistent with symptoms of insomnia are reported by up to 90% of MDD patients (Palagini et al., 2013; Riemann, Berger, & Voderholzer, 2001) and may play a key role in the pathology of the illness (Alvaro, Roberts, & Harris, 2014; Baglioni et al., 2011). Aside from subjective sleep complaints, polysomnographic sleep research has revealed that up to 70% of MDD patients display a consistent pattern of neurobiological changes in their sleep (Riemann et al., 2001), the most reliable of which include a marked increase in REM sleep duration and density, and a decrease in REM sleep latency (Fig. 1; Luik et al., 2015; Nutt, Wilson, & Paterson, 2008; Palagini et al., 2013; Pillai et al., 2011; Schulz, Lund, Cording, & Dirlich, 1979).

**Fig. 1.**

Graphic representation of sleep architecture in healthy controls and depressed patients. Amongst other characteristics, sleep architecture in depression is associated with: **(a)** reduced rapid eye movement (REM) sleep latency (the interval between sleep onset and the first period of REM sleep; Schulz, Lund, Cording & Dirlich, 1979), and **(b)** increased REM sleep duration, which is most notable in the first REM sleep period (Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013). N1, N2 and N3 – stages of non-REM (NREM) sleep.

In healthy humans, non-REM (NREM) and REM sleep alternate in cycles of approximately 90 minutes. The length of this cycle remains consistent throughout the night, however the ratio of NREM – REM sleep changes, with REM sleep becoming progressively more abundant with each cycle (see Fig. 1). Although the functional reasons for this late night increase in REM sleep are elusive (Walker, 2009), it is clear that REM sleep propensity is tightly regulated by circadian rhythms (Pace-Schott & Hobson, 2002). There is believed to

be a relationship between depression and circadian rhythm disturbances (Bunney & Bunney, 2013; Etain, Milhiet, Bellivier, & Leboyer, 2011; Kronfeld-Schor & Einat, 2012), supported by a large scale study demonstrating a strong correlation between extreme chronotypes – a key feature of circadian rhythm disturbance – and depressive symptoms (Levandovski et al., 2011). While the neurotransmitter systems related to REM sleep alterations in depression remain poorly understood, it has been hypothesised that circadian rhythm disturbances may be implicated in the increased REM sleep duration and density associated with MDD (Palagini et al., 2013). Indeed, polymorphisms and haplotypes in several circadian clock genes – genes involved in the regulation of circadian rhythms – have been linked to depression susceptibility (Bunney & Bunney, 2013; Etain et al., 2011; Utge et al., 2010), some of which have also been linked to extreme chronotypes including period homologue 3 (*PER3*; Hida et al., 2014; Parsons et al., 2014), circadian locomotor output cycles kaput (*CLOCK*; Paul, McAlonan, & Banerjee, 2011) and casein kinase 1 epsilon (*CSNK1E*; Takano et al., 2004). It is important to note however that this area of research is in its infancy, and researchers are yet to provide strong evidence for a causal role of either circadian rhythm disturbances or variants in circadian clock genes in the development of MDD.

Given that the spectral composition of sleep is highly heritable (Ambrosius et al., 2008), it is perhaps unsurprising that some of the REM sleep characteristics exhibited by depressed patients, most notably increased REM sleep density, are also present in their first-degree relatives (Lauer, Schreiber, Holsboer, & Krieg, 1995; Modell, Ising, Holsboer, & Lauer, 2002; Pillai et al., 2011). Indeed, the notion that REM sleep density is under strong genetic control is supported by work in mice who exhibit “almost perfect trait-like stability” of REM sleep density across several days (Fulda et al., 2011). Interestingly however, the presence of increased REM sleep density in first-degree relatives of MDD patients has been shown to predict development of later depressive episodes (Modell et al., 2002; Modell &



Lauer, 2007; Steiger & Kimura, 2010). In a meta-analysis of 56 studies, Pillai and colleagues (2011) report that some of the sleep changes exhibited in MDD such as increased REM sleep duration are restricted to the depressive episode, however increased REM sleep density often remains stable throughout remission (Pillai et al., 2011). Importantly, increased REM sleep density has been shown to predict poor clinical response to treatment in MDD (Buysse et al., 1999; Clark et al., 2000; Modell & Lauer, 2007), and its persistence beyond depressive episodes may heighten vulnerability to relapse (Mendlewicz, 2009). Collectively, these findings suggest that increased REM sleep density may be associated with increased vulnerability to depression onset and relapse.

It is well reported that most antidepressant drugs considerably inhibit REM sleep, thus increasing REM sleep latency or decreasing REM sleep density and duration (Mayers & Baldwin, 2005; Murck et al., 2003; Palagini et al., 2013; Steiger & Kimura, 2010; Thase, 2006; Vogel, Buffenstein, Minter, & Hennessey, 1990). Furthermore, research in humans and animals demonstrates that selective REM sleep deprivation can produce rapid antidepressant effects (Benedetti & Colombo, 2011; Maturana et al., 2015). Findings such as these have led researchers to hypothesise that REM sleep suppression may be an essential component of any effective form of MDD therapy (Vogel, McAbee, Barker, & Thurmond, 1977). However, this notion may be refuted by studies which report that a few pharmaceuticals effective in the treatment of MDD such as the tricyclic antidepressant trimipramine, the norepinephrine-dopamine reuptake inhibitor bupropion, and the serotonin reuptake enhancer tianeptine, do not inhibit REM sleep (Murck et al., 2003; Nofzinger et al., 1995; Sonntag et al., 1996). In addition, the inhibitory effects of antidepressants on REM sleep are robust early in treatment, but gradually return towards baseline with long-term treatment (Wilson & Argyropoulos, 2005). Indeed, it is unclear whether the antidepressant effects reported in selective REM sleep deprivation studies are due to the absence of REM sleep or simply the disruption of

NREM sleep homeostasis. For example, it has been reported that the selective disruption of NREM sleep can also produce antidepressant effects (Grözing, Kögel, & Rösche, 2002; Landsness, Goldstein, Peterson, Tononi, & Ruth, 2011). Overall, there appears to be some link between the suppression of REM sleep and the relief of depressive symptoms. However, it is clear that REM sleep suppression is not an exclusive mechanism by which antidepressant treatments reduce depressive symptoms.

### **3. The Role of Amygdala Function in Depression**

The emotional and cognitive disturbances which characterise MDD are thought to be related to structural and functional alterations in several neural networks, particularly involving regions of the prefrontal cortex and closely related limbic, thalamic and striatal structures (for reviews see: Auerbach, Webb, Gardiner, & Pechtel, 2013; Drevets, Price, & Furey, 2008; Price & Drevets, 2012). The present review will provide a brief overview of the research exploring the relationship between amygdala function and depression, due to the involvement of the amygdala in emotional memory formation.

In healthy participants the amygdala is activated in response to the presentation of both negative (Kumfor, Irish, Hodges, & Piguet, 2013; Stark et al., 2007) and positive (Kensinger & Schacter, 2006; Vrticka, Lordier, Bediou, & Sander, 2014) emotional material, however in participants with depression the amygdala is more sensitive to aversive stimuli, and less sensitive to positive stimuli. For example, whilst viewing masked facial expressions healthy participants exhibit stronger bilateral amygdala responses to happy relative to sad expressions, whereas the opposite pattern is demonstrated by MDD patients (Stuhrmann et al., 2013; Suslow et al., 2010). In comparison to healthy controls, depressed patients also demonstrate greater right amygdala activation for sad expressions (Costafreda et al., 2013;

Stuhrmann et al., 2013; Suslow et al., 2010). Complementary findings have also been reported in subclinically depressed participants who, relative to never-depressed participants, show increased bilateral amygdala activation in response to negative emotional words, a neural pattern which correlates with symptom severity (Laeger et al., 2012).

Evidence suggests that affective reactivity in the amygdala may be influenced by several monoamine systems, including serotonin (5-HT), norepinephrine (NE), and dopamine (DA; Costafreda et al., 2013; Cousijn et al., 2010; Dannlowski et al., 2010; Delaveau et al., 2009; Rasch et al., 2009). Initially, a simple lack of monoamines was thought to cause depressive symptoms, however the role of monoamines in MDD has been shown to be much more complex than this (Delgado, 2000; Hirschfeld, 2000). Nonetheless, a meta-analysis of 90 monoamine depletion studies suggests a probable influence of 5-HT, NE and DA in depression vulnerability (Mason & Schene, 2007). Furthermore, the importance of 5-HT in MDD treatment is evidenced by the use of selective serotonin re-uptake inhibitors (SSRIs) as the current first-line treatment option for MDD patients (Davidson, 2010; Dold et al., 2016), although the efficacy of SSRIs in MDD treatment is doubted by some researchers (Kirsch, 2014; Rücker & Jamil, 2015). Examining the relationship between monoamines and altered patterns of functional amygdala responsivity to affective stimuli may improve our understanding of both monoamines and genetic variation in depression vulnerability. Whilst we acknowledge that both functional amygdala activity and depression is influenced by multiple neuromodulator systems, in this review we focus primarily on 5-HT as it is the most widely studied with regards to depression.

Neuroimaging research demonstrates that short-term SSRI treatment remediates the amygdala hyperactivity typically exhibited by MDD patients in response to fearful facial expressions (Godlewska, Norbury, Selvaraj, Cowen, & Harmer, 2012). Furthermore, genetic

research suggests that healthy carriers of the low-expressing short (S) allele in the 5-HT transporter-linked polymorphic region (5-HTTLPR) exhibit greater amygdala activation in response to negative emotional faces (Dannlowski et al., 2010; Lonsdorf et al., 2011; Pezawas et al., 2005), and aversive images (Heinz et al., 2005), relative to long (L) allele homozygotes. Similar results have also been observed in clinical populations, where S allele carriers with a diagnosis of MDD exhibit greater amygdala activations in response to negative facial expressions relative to both healthy and depressed non-carriers (Costafreda et al., 2013).

Recent research demonstrates that relative to low-risk probands, offspring at high familial risk of MDD are four times more likely to be carriers of the 5-HTTLPR S allele (Talati et al., 2015). These findings support other studies and meta-analyses which suggest a relationship between the 5-HTTLPR S allele and MDD risk (Bogdan, Agrawal, Gaffrey, Tillman, & Luby, 2014; Kim et al., 2007; Kiyohara & Yoshimasu, 2010), although other meta-analyses have failed to replicate this finding (e.g. Risch et al., 2009). Moreover, first-degree relatives of MDD patients have been observed to exhibit greater amygdala activity in response to negative emotional material relative to participants at low-risk for MDD (Monk et al., 2008; van der Veen, Evers, Deutz, & Schmitt, 2007). The 5-HTTLPR S allele is associated with decreased transcriptional efficiency of the promoter (Lesch et al., 1996), and increased available synaptic 5-HT acting on excitatory 5-HT receptor subtypes (Rainnie, 1999). Alterations such as these in the serotonergic system are believed to underlie the amygdala hyper-responsivity to negative emotional material observed in S allele carriers (Hariri et al., 2002), which may be one of the neural bases for the additional risk of developing depression in this population.

It is important to emphasize that the altered patterns of functional amygdala activity described in both MDD patients and 5-HTTLPR S allele carriers are not necessarily the direct product of hard-wired alterations in emotional reactivity. Rather, it is thought that the increased amygdala response exhibited by these populations may reflect altered affective attentional processes which are pre-tuned and malleable according to context and motivational salience (Cunningham, Van Bavel, & Johnsen, 2008; Todd, Cunningham, Anderson, & Thompson, 2012).

#### **4. The Role of REM Sleep and Amygdala Function in Emotional Memory**

Physiological and behavioural evidence supports a role for REM sleep in emotional memory consolidation, which may aid our understanding of REM sleep alterations in the onset and maintenance of MDD. Neural regions implicated in emotional memory processing during wake, in particular the amygdala, entorhinal cortex and medial prefrontal cortex, are reactivated during REM sleep (Maquet et al., 1996; Nir & Tononi, 2010; Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997). Indeed, preclinical evidence suggests that the amygdala may even play a crucial role in REM sleep regulation (Calvo, Simón-Arceo, & Fernández-Mas, 1996; Sanford, Parris, & Tang, 2002; Sanford, Yang, Liu, & Tang, 2006). Furthermore, REM sleep is characterised by the occurrence of dominant hippocampal theta oscillations (Buzsáki, 2002) which are believed to allow coherence between limbic regions within the medial temporal lobe such as the amygdala and hippocampus (Walker & van der Helm, 2009) and may directly reflect the selective processing of emotional memory traces (Hutchinson & Rathore, 2015). According to the ‘sleep to forget and sleep to remember’ (SFSR) hypothesis – a theoretical framework in which sleep has differential effects on the strength and affective tone of emotional memories – REM sleep provides an “optimum

biological theatre” for the consolidation of emotionally salient memories (Walker & van der Helm, 2009). The ‘sleep to forget’ component of the SFSR hypothesis postulates that REM sleep diminishes the emotional tone associated with affective memories, providing a source of catharsis. Although the evidence for this element of the hypothesis is not entirely conclusive (for review see: Landmann et al., 2015) evidence in support of the notion that REM sleep selectively consolidates emotional memories (the ‘sleep to remember’ component of the SFSR hypothesis) is more abundant.

Behavioural research in support of the ‘sleep to remember’ element of the SFSR hypothesis reports that a group of healthy students selectively deprived of REM sleep show impaired next-day recognition performance for negative images encoded pre-sleep, relative to a control group deprived of NREM slow wave sleep (SWS; Wiesner et al., 2015). Importantly, the two groups did not differ in their recognition performance for neutral images. This emotion-specific effect of REM sleep corroborates earlier work which found that three hours of late night REM dominant sleep facilitates the consolidation of negative images (Groch, Zinke, Wilhelm, & Born, 2015) and information within negative stories (Wagner, Gais, & Born, 2001), relative to three hours of sleep obtained in the first half of the night where REM sleep is less abundant. Correlational analyses have yielded similar results, finding that the amount of time spent in REM sleep across a 12-hour retention interval correlates positively with recall performance for negative but not neutral objects within complex images (Payne et al., 2012). Complementary findings report that these effects can also emerge across a shorter time frame, demonstrating that the proportion of time spent in REM sleep during a 90-minute daytime nap correlates positively with recognition performance for negative images (Nishida et al., 2009). Collectively, these results suggest that REM sleep selectively consolidates emotional information and that its role in this process is active, rather than simply protective against the forgetting of emotional material.

While it is clear that the amount of time spent in REM sleep during consolidation intervals influences emotional memory performance, the impact of REM sleep density on emotional memory consolidation has received comparatively less empirical attention. Nonetheless, a recent study by Gilson and colleagues (2015) reports that in healthy participants greater REM sleep density during a 90-minute morning nap was associated with greater recall performance for sad emotional stories, but not neutral stories (Gilson et al., 2015). Human neuroimaging studies reveal that rapid eye movements (REMs) during REM sleep are closely associated with transient activity in limbic regions such as the amygdala and parahippocampal gyrus (Abe, Ogawa, Nittono, & Hori, 2004; Ioannides et al., 2004). Amygdala activations time-locked to REM sleep REMs have also been detected using stereoelectroencephalograph (SEEG; Corsi-Cabrera et al., 2016) and single-neuron recording (Andrillon, Nir, Cirelli, Tononi, & Fried, 2015) methods. These findings suggest that REM sleep density may be a surrogate marker of limbic neural activity during REM sleep, and might be associated with emotional memory processing. Indeed, a positron emission tomography (PET) study by Nofzinger and colleagues (2004) reveals that relative to control participants, depressed patients exhibit greater activation of limbic and paralimbic structures from waking to REM sleep (Nofzinger et al., 2004). These differences in neural activation during REM sleep may be related to differences in REM sleep density between the two participant groups.

It has been suggested that the emotional arousal elicited by affective stimuli at the time of encoding “tags” an event as salient, leading to its prioritised consolidation during REM sleep (Bennion, Payne, & Kensinger, 2015). According to influential theories, the amygdala plays a key role in this mechanism through interactions with neural regions involved in emotion, vision and learning including the posterior insula, lateral occipital cortex and hippocampus (Hermans et al., 2014; Markovic, Anderson, & Todd, 2014; McIntyre,

McGaugh, & Williams, 2012). In support of these hypotheses, work in rats has shown that artificial stimulation of the basolateral amygdala enhances the recognition of novel objects following a 24 hour retention interval (Bass, Nizam, Partain, Wang, & Manns, 2014; Bass, Partain, & Manns, 2012). These findings corroborate a recent human case study which reports that lesions in the left amygdala cause encoding and long-term memory deficits for emotionally arousing words, but have no effect on memory for neutral words (Claire, Sophie, Claudia, Philippe, & Eliane, 2015). Neuroimaging research in healthy participants reveals a positive correlation between bilateral amygdala activity during the encoding of emotional films and recall performance for film content three weeks later (Cahill et al., 1996; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000). Similar results have been found in MDD patients who, relative to control participants, exhibit increased right amygdala activity in response to negative emotional images which predicts superior recall for those images one week later, and correlates with depressive symptom severity (Hamilton & Gotlib, 2008).

## **5. The ‘Affect Tagging and Consolidation’ (ATaC) Model**

Research which demonstrates that many compounds with antidepressant properties suppress REM sleep (Mayers & Baldwin, 2005; Steiger & Kimura, 2010; also see: Murck et al., 2003; Nofzinger et al., 1995; Sonntag et al., 1996), considered alongside evidence that REM sleep duration and density is associated with the consolidation of negative memories (Gilson et al., 2015; Groch et al., 2015; Nishida et al., 2009; Payne et al., 2012; Wagner et al., 2001; Wiesner et al., 2015), has led researchers to speculate that REM sleep alterations may underlie the emotional memory bias observed in depressed patients (Walker & van der Helm, 2009; Walker, 2009). However, the majority of studies directly investigating the effect of REM sleep on emotional memory consolidation focus exclusively on comparisons between

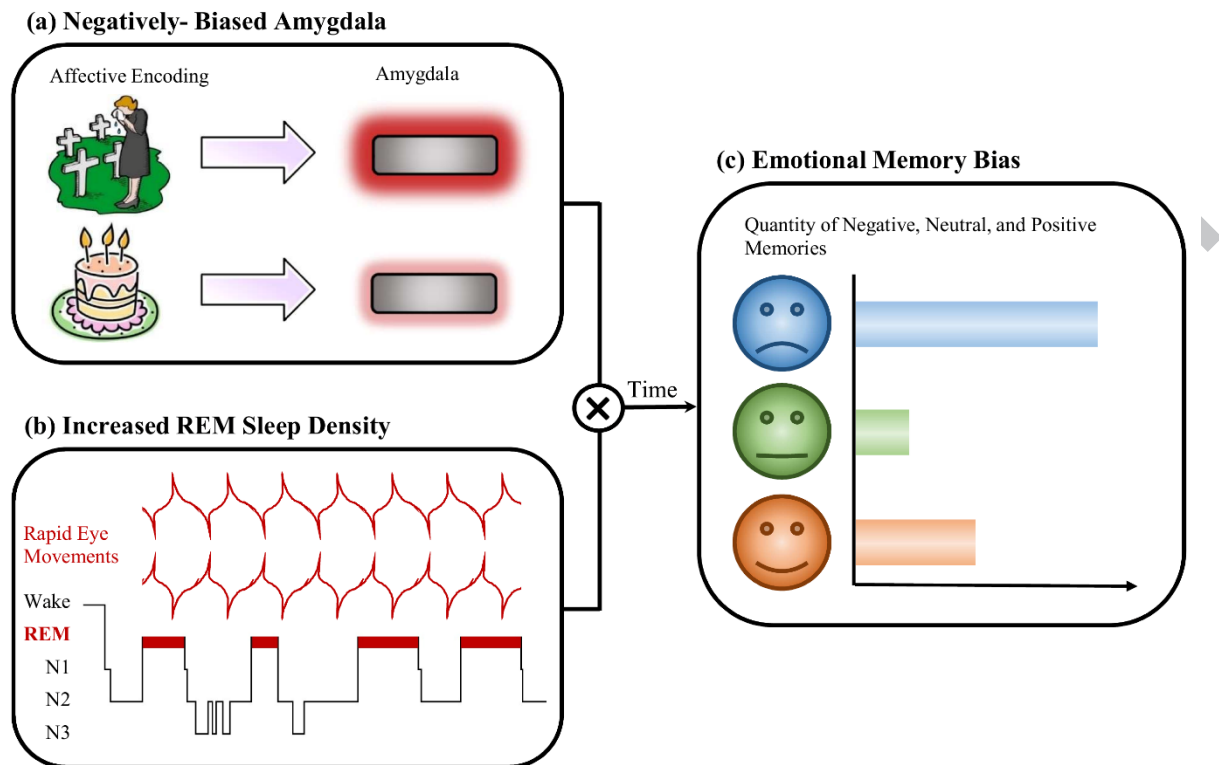


recognition performance for neutral and negatively salient stimuli (however see: Cairney, Durrant, Power, & Lewis, 2015), ignoring the possibility that REM sleep may also play a role in the consolidation of positive memories. The amygdala is believed to exert its influence on memory consolidation based on its initial activation during the encoding of emotional information (Markovic et al., 2014), which is thought to underlie the emotion-specific consolidation effects of REM sleep (Bennion et al., 2015; Goldstein & Walker, 2014; Walker & van der Helm, 2009). However, as described earlier, in healthy participants the amygdala responds to both positive and negative material (Kensinger & Schacter, 2006; Vrticka et al., 2014). To this end, it is likely that in the absence of excessive emotional tagging of negative material associated with altered patterns of functional amygdala activity, an increase in REM sleep duration or density would lead to a generally enhanced emotional memory, rather than the negative memory bias observed in depression. Consequently, increased REM sleep density as a vulnerability factor for depression may depend on an interaction with biased encoding mechanisms related to negatively-biased amygdala activity.

As previously discussed, there is a probable link between the 5-HTTLPR S allele and MDD vulnerability (Munafò, Durrant, Lewis, & Flint, 2009; Talati et al., 2015; however see: Risch et al., 2009), which may be related to altered patterns of functional amygdala activity (Costafreda et al., 2013). There is also abundant evidence to suggest that amygdala hyperactivity towards negative stimuli is related to long-term negative memory bias in depression (Hamilton & Gotlib, 2008). Importantly however, negatively-biased amygdala activity is also exhibited by non-depressed 5-HTTLPR S allele carriers (Dannlowski et al., 2010; Heinz et al., 2005; Lonsdorf et al., 2011; Pezawas et al., 2005) and first-degree relatives of MDD patients (Monk et al., 2008). Evidence suggests that modulatory effects of the amygdala on memory are absent during immediate recall (Bass et al., 2014, 2012; Claire et al., 2015), and only emerge at recall sessions at least 24-hours after immediate testing,

inferring that the amygdala may depend on overnight consolidation mechanisms to exert its influence on long-term memory.

Founded on these notions, our ‘affect tagging and consolidation’ (ATaC) model (Fig. 2) posits that amygdala hyperactivity during the encoding of aversive life events – and hypoactivity during the encoding of positive life events – could cause negative memories to be tagged as highly salient, ensuring that they are prioritised above positive memories during overnight consolidation. This process may be mediated by attentional biases which have been associated with both alterations in monoamine availability (Fox & Standage, 2012; Todd et al., 2013) and MDD (Peckham, McHugh, & Otto, 2010; Yang, Zhang, Ding, & Xiao, 2016; also see: Blaut, Paulewicz, Szastok, Prochwicz, & Koster, 2013; Everaert et al., 2014). If complemented by increased REM sleep duration or density, the amygdala may then be provided surplus opportunity to exert its influence on emotional memory consolidation. This could cause an excessive amount of negative material to be stabilised in long-term memory, ensuring that the negative aspects of events are remembered in most detail. Over an extended period of time the result of this process would be an autobiographical memory saturated with detailed accounts of negative experiences and a marked absence of positive memories. It is clear how this brain state could manifest as depressive symptoms and promote other depressive traits which could reinforce such symptoms.

**Fig. 2.**

The affect tagging and consolidation (ATaC) model. This diagram provides a visual representation of enhanced amygdala activation in response to negative emotional experiences interacting with increased rapid eye movement (REM) sleep density to form an emotional memory bias over time. Panel (a) represents increased activation in the amygdala (depicted as a deeper red glow) during the encoding of negative stimuli (funeral) relative to positive stimuli (birthday). Panel (b) represents increased REM sleep density, which would lead to a general enhancement in emotional memory according to the ATaC model. Panel (c) represents negatively-biased amygdala activity interacting with increased REM sleep density to cause a negative memory bias, which is believed to increase vulnerability to depression (Beck, 1967; Everaert, Koster, & Derakshan, 2012). N1, N2 and N3 – stages of non-REM (NREM) sleep.

The ATaC model predicts that the excessive emotional tagging of negative material associated with negatively-biased amygdala activity may not manifest as a clinically significant memory bias if REM sleep, which stabilises negative experiences in long-term memory (Groch et al., 2015; Nishida et al., 2009; Payne et al., 2012; Wagner et al., 2001; Wiesner et al., 2015; also see: Wagner, Hallschmid, Rasch, & Born, 2006), is adequately

regulated. As we have seen, REM sleep propensity is tightly regulated by circadian rhythms (Pace-Schott & Hobson, 2002) which are thought to be disturbed in depression (Bunney & Bunney, 2013; Etain et al., 2011; Kronfeld-Schor & Einat, 2012). It is believed that circadian rhythms are generated and regulated by circadian clock genes, which may play a role in depression vulnerability (Bunney & Bunney, 2013; Etain et al., 2011; Utge et al., 2010) and could plausibly be related to the REM sleep alterations characteristic of MDD (Palagini et al., 2013). According to the ATaC model, variations in genes which promote an increase in REM sleep density may act as a risk factor for depression by allowing surplus opportunity for emotional memories to be consolidated, but only if it is adjunct to excessive tagging of negative emotional material associated with negatively-biased amygdala activity. We argue that these two vulnerability factors for MDD – increased REM sleep density and negatively-biased amygdala activity – are independent of each other, and each have their own set of causes, but interact to create a long-term negative memory bias which manifests as depressive symptoms over time. Given that increased REM sleep duration is found in currently depressed patients, but not remitted patients or first-degree relatives of patients (Pillai et al., 2011), we predict that an increase in REM sleep duration could support the maintenance of depressive symptoms once established.

The importance of interactions between variants in clock genes and genes which modulate monoaminergic pathways such as the 5-HT system may go some way towards explaining the weak association between ‘risk genes’ and the prevalence of depression (Lohoff, 2010; Mitjans & Arias, 2012), whilst accounting for the comparatively high heritability of MDD (Agrawal, Jacobson, Gardner, Prescott, & Kendler, 2004; Kendler, Gardner, Neale, & Prescott, 2001; Sullivan, Neale, & Kendler, 2000). It should be noted however that in order to focus on core elements of the ATaC model we have discussed in this review only the fundamental mechanisms underlying negatively-biased emotional memory;

notwithstanding, we acknowledge that the overarching cause of depression is likely to be much more complex. For example, the ATaC model looks exclusively at endogenous mechanisms and therefore does not take into account environmental factors such as childhood stress or trauma, which are likely to interact with the 5-HTTLPR and other ‘risk genes’ in the development of some forms of depression (Kim et al., 2007; Munafò et al., 2009). Furthermore, although the ATaC model discusses the role of amygdala function in emotional memory and MDD, there is substantial evidence that other neural structures which modulate emotional memory are implicated in depression vulnerability (for analyses see: Beck, 2008; Disner, Beevers, Haigh, & Beck, 2011). Finally, as previously mentioned this review has focused primarily on the influence of the 5-HT system and the 5-HTTLPR on functional amygdala activity and depression vulnerability. However, we acknowledge the importance of genes which influence other monoamine systems such as *ADRA2B* and *COMT* in modulating affective amygdala function, emotional memory, and potentially depression vulnerability (Cousijn et al., 2010; Lonsdorf et al., 2011; Naudts, Azevedo, David, van Heeringen, & Gibbs, 2012; Shen et al., 2014; Todd, Palombo, Levine, & Anderson, 2011).

## 6. Future Directions

This article has reviewed the roles of REM sleep and the amygdala in emotional memory consolidation, and applied these insights to the understanding of REM sleep alterations and negatively-biased amygdala activity in the onset and maintenance of MDD. We have introduced the ATaC model which proposes testable hypotheses centred around the notion that interactive effects between altered patterns of functional amygdala activity and increased REM sleep density may play a role in the development of emotional memory bias and subsequent depressive symptoms.

Although derived from a substantial body of evidence, our model is hypothetical at present, and future research into the interplay between amygdala function and REM sleep, and its influence on memory consolidation, will determine its validity. In rats, such work could integrate selective REM sleep deprivation paradigms (e.g. Hunter, 2015) with direct amygdala stimulation techniques (e.g. Bass et al., 2014, 2012) to determine whether the effects of amygdala activation at encoding and subsequent REM sleep on memory are indeed interactive as hypothesised by the ATaC model. In humans, similar studies could investigate the effect of REM sleep, and sleep deprivation, on memory consolidation for positive and negative emotional material in carriers of the 5-HTTLPR S allele relative to L allele homozygotes. This strategy could reveal the respective contributions of negatively-biased amygdala activity and REM sleep duration and density to emotional memory biases. Further research should also focus on identifying genetic variants which may contribute to the increase in REM sleep density exhibited by MDD patients and their first-degree relatives. The discovery of these variants would allow researchers to explore their interaction with the 5-HTTLPR in long-term emotional memory biases and overall depression vulnerability.

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The 'Affect Tagging and Consolidation' (ATaC) Model of Depression Vulnerability:

Highlights

- Negatively-biased amygdala activity is related to encoding of negative stimuli.
- Increased REM sleep causes emotional memories to be consolidated more readily.
- These two mechanisms may interact to increase vulnerability to depression.
- There is evidence that these mechanisms have separate genetic influences.
- We present the Affect Tagging and Consolidation (ATaC) model of depression.